PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X/16846M

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

22 NOV 2005

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/000021	18.01.2005	22.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D295/08, C07D209/46, C07D307/83, C07D209/48, C07D311/78, C07D409/04, C07D333/64, C07D295/18,

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 33,34

because:

☒ the said international application, or the said claims Nos. 33,34 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18,21,24,29-32,39,41,45-51,54,56,61-63
	No:	Claims	19,20,22,23,25-28,33-38,40,42-44,52,53,55,57-60
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-63
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

AD SECTION III:

1. For the assessment of the present claims 33 and 34 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

   Claims 33 and 34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

AD SECTION V:

1. The following documents have been considered:
   - D1: GRESE, TIMOTHY A. ET AL: "Structure-Activity Relationships of Selective Estrogen Receptor Modulators: Modifications to the 2-Arylbenzothiophene Core of Raloxifene" JOURNAL OF MEDICINAL CHEMISTRY , 40(2), 146-167 CODEN: JMCMAR; ISSN: 0022-2623, 1997, XP002050782
   - D2: KAUFFMAN, RAYMOND F. ET AL: "Hypocholesterolemic activity of raloxifene (LY139481): pharmacol. characterization as a selective estrogen receptor modulator" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS , 280(1), 146-153 CODEN: JPETAB; ISSN: 0022-3565, 1997, XP002330951
   - D3: EP-A-0 729 956 (ELI LILLY AND COMPANY) 4 September 1996 (1996-09-04)
   - D4: EP-A-0 703 228 (ELI LILLY AND COMPANY) 27 March 1996 (1996-03-27)
   - D5: EP-A-0 895 989 (ELI LILLY AND COMPANY) 10 February 1999 (1999-02-10)
   - D6: EP-A-0 761 659 (ELI LILLY AND COMPANY) 12 March 1997 (1997-03-12)
   - D7: US-B1-6 204 286 (CAMERON KIMBERLY O ET AL) 20 March 2001 (2001-03-20)

2. Claims 19, 20, 22, 23, 25-28, 33-38, 40, 42-44, 52, 53, 55 and 57-60 do not appear to be novel, having regard to D1, which discloses on page 148 compound 10k and on page 149 compounds 23a-23g and compound 7 disclosed on page 151 of D2. These compounds are selective estrogen receptor modulators (SERM).
The compounds disclosed in D3 to D6 differ from the present compounds mainly on account of the substitution of the phenyl group situated at position 2 of the thiophenyl/naphthyl groups.
The compounds disclosed in D7 differ on account of the tetrahydronaphthyl nucleus, which however can be substituted by phenyl substituted by hydroxyalkyl.
The compounds disclosed in D3 to D7 possess similar pharmacological activities as the present compounds, i.e. they are selective estrogen receptor modulators and/or can be used in the treatment of endometriosis and uterine fibrosis.
Accordingly, the present application does not satisfy the requirements of Article 33(2) PCT, therefore, the Applicant is invited to submit claims which overcome these objections.

3. Closest prior art comprises the compounds disclosed in D1 to D7, which possess similar pharmacological properties as the present compouds.
The problem to be solved was to provide further SERM compounds useful for treating endometriosis and uterine fibrosis.
The Applicant has shown the alleged activities on pages 83-89 of the description, however, having regard to the closely related, i.a. novelty destroying, prior art, it is considered that the skilled person would have expected the compounds claimed to possess such activities.
Whether or not the structural modifications of the state of the art are associated with an improvement at all is a fundamental aspect of inventive step. Unless evidence refutes the assumption that the small modifications made are not unexpectedly associated with a significant improvement in the property relevant to the solution of the stated problem, the presumption prevails that the compounds represent only predictable effects and are therefore obvious. The solution of the problem of merely providing further compounds showing SERM activities does not involve an inventive step.
Thus in the absence of any unexpected effect or advantage of the compounds claimed an inventive step as required by Article 33(3) PCT cannot be acknowledged.

The Applicant is requested to demonstrate, preferably by means of comparative tests, whereon an inventive step could be based.

4. No objections with regard to Article 33(4) PCT arise for claims 1-32 and 35-63, however, see Section III above.

AD SECTION VII:

1. Claim 18 comprises all the features of claims 1 and 19 and is therefore not appropriately formulated as a claim dependent thereon (Rule 6.4 PCT).

2. In claim 52 the definition for Y^1 is superfluous and should be deleted.